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Evaluation of Serum Visceral Protein Levels as Indicators of Nitrogen Balance in Thermally Injured Patients*

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ABSTRACT. The use of serum visceral protein concentrations as predictors of nitrogen balance was assessed during the first 4 weeks following thermal injury. The correlation between nitrogen balance and serum albumin was not significant. Statistically significant correlations were found between nitrogen balance and serum prealbumin, retinol-binding protein, and transferrin. However, even the best correlation (retinol-binding protein, $r = 0.388$) was too weak to permit prediction of nitrogen balance on the basis of the visceral protein concentration. The correlation between change in direction of nitrogen balance and change in direction of protein concentration over time showed all four visceral proteins to be poor predictors of change

in nitrogen balance. The efficiency was less than 50% for each visceral protein. Stepwise multiple regression analysis performed to determine which indices were most closely correlated with nitrogen balance showed that a calculation using readily available information (nitrogen intake, postburn day, percent total body surface burned, and age) provided better prediction of nitrogen balance ($r = 0.765$) than any of the visceral protein concentrations. In view of these findings, measurement of serum visceral protein concentrations to monitor adequacy of nutritional support seems an unwarranted expense in patients with thermal injury. (*Journal of Parenteral and Enteral Nutrition* 15:440-444, 1991)

The importance of providing adequate calories and protein for the healing of serious burn injury is well recognized. An optimal method to monitor the adequacy of nitrogen intake, however, remains to be defined. Measurement of nitrogen balance is an accepted method of determining the efficacy of a nutritional regimen, but accurate determination of nitrogen intake and output is labor intensive and impractical for general clinical use.

Several researchers have suggested that measures of serum visceral proteins can be used to predict nitrogen balance and that this method is useful in assessing the efficacy of nutritional support regimens. Starker et al¹ demonstrated an association between decreased serum albumin levels and negative nitrogen balance. Comparing changes in measures of serum albumin, prealbumin, transferrin, and retinol-binding protein with changes in nitrogen balance, Church and Hill² showed that increases and decreases in prealbumin levels were correlated with positive and negative changes in nitrogen balance in general surgical patients. Tuten et al³ reported positive correlations between change in nitrogen balance and change in both prealbumin and transferrin levels in patients receiving parenteral or enteral nutrition. Both

Fletcher et al⁴ and Smale et al⁵ reported that changes in serum transferrin concentrations correlated with changes in nitrogen balance.

In view of these reports, we felt serial measures of these serum visceral proteins might also provide a method of predicting nitrogen balance in thermally injured patients.

The purpose of this study was to determine whether changes in serum levels of albumin, prealbumin, transferrin, or retinol-binding protein are correlated with changes in nitrogen balance in patients with thermal injury.

METHODS

Nitrogen balance and serum protein levels were measured in 10 adult patients with thermal injuries involving at least 20% of total body surface, admitted to the US Army Institute of Surgical Research (ISR) between November 1987 and March 1988. Data collection was initiated on postburn day 5, after stabilization of fluid status, and then repeated every 3 days until postburn day 30.

Dietary Regimens

Daily energy requirements were estimated for studied patients by indirect calorimetry or by using a formula derived at the ISR based on earlier indirect calorimetry data. Protein requirements were calculated to provide a kilocalorie to nitrogen ratio of 150:1. Patients were provided regimens designed to meet these goals using oral diets, enteral feedings via nasogastric tube, total paren-

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The research protocol was approved by Medical Research and Development Command and informed consent was obtained from each patient prior to participation in the study.

92 1 16 107

teral nutrition, or combinations of these feeding modes. Daily calorie counts were calculated to determine the percentage of the requirement met each day.

Serum Visceral Proteins

Serum samples were analyzed for albumin, transferrin, prealbumin, and retinol-binding protein. Serum albumin assays were performed on an SMA autoanalyzer (Chemistry Autoanalyzer Instrumental Laboratory, Lexington, MA). Serum transferrin, prealbumin, and retinol-binding protein were measured using radioimmunoassay techniques.

Nitrogen Balance

Nitrogen intakes for each 24-hour period were calculated from records of the parenteral and enteral nitrogen administered. Oral diet data were obtained by weighing quantities of foods served to and rejected by patients. Food composition data were obtained from United States Department of Agriculture data or from manufacturers' information for commercial products.

Twenty-four-hour urine samples were collected and aliquots were analyzed for total nitrogen using a digital nitrogen detector (Antek Instruments Inc., Houston, TX). Nitrogen loss across the burn wound was estimated using the formula of Waxman et al⁶ with a correction factor for the effect of silver sulfadiazine. The percent of remaining open wound was calculated daily. The formula used was:

$$g \text{ nitrogen} = 0.1 \times \text{BSA} \times \% \text{TBSB} \times 0.8$$

BSA = Body surface area in square meters

%TBSB = The percentage of the total
body surface area with open wound

An estimate of 2 g/d was used for fecal loss of nitrogen. Nitrogen balances were calculated by subtracting nitrogen output (urine + wound + 2) from nitrogen intake.

Statistical Analysis

Regression analysis was used to evaluate the relationship between serum visceral protein concentrations and nitrogen balance.

Changes in nitrogen balance across time were determined for each subject. Changes in each serum visceral protein concentration were calculated for each subject at corresponding time points. The directions and magnitudes of these changes were determined. A change of at least 10% was considered a significant difference and was recorded as either a positive or negative change. Changes of less than 10% were recorded as no change. A change of nitrogen balance and a serum visceral protein concentration in the same direction at the same time point was considered a correct prediction. The number of correctly predicted positive and negative nitrogen balance changes were determined for each subject for each serum visceral protein. An overall efficiency for each serum protein was determined as the number of correctly predicted nitrogen balance changes divided by total nitrogen balance changes multiplied by 100.

RESULTS

Ten patients (nine men and one woman) were studied (Table I). Eight of the 10 patients had at least one operative procedure performed during the study period and half of the patients had more than one such procedure. Nine of the 10 patients were transfused at least 1 unit of blood during the study period and seven of these patients received multiple transfusions.

The study population was purposely varied to assess the applicability of this method of predicting nitrogen balance in the usual clinical situation. Detailed information regarding the patient population is presented in Table II.

Nitrogen intake and balance for postburn day (PBD) 5, 11, 20, and 29 are tabulated in Table III. Nitrogen balance was initially negative in all but one subject. As a general trend, nitrogen balance became more positive with time, but individual variation was seen. For example, patient 9 had a more negative balance on PBD 20 than on PBD 11 because his nutritional regimen was interrupted for surgery. Seven of the patients demonstrated neutral or positive balance by the end of the study period.

Regression data for each serum visceral protein *vs* nitrogen balance are presented in Figure 1. Serum transferrin, retinol-binding protein, and prealbumin showed statistically significant positive correlations with nitrogen balance, whereas serum albumin did not. Retinol-binding protein showed the best correlation of the four proteins measured ($r = 0.388$), but even retinol-binding protein would account for only 15% of the observed variation in nitrogen balance and did not correlate at a level that could be used for clinical prediction of nitrogen balance.

Stepwise multiple regression analysis was performed to determine what parameters could best predict nitrogen balance. Variables tested included age, percentage of the total body surface burned, postburn day, nitrogen intake, and serum albumin, transferrin, retinol-binding protein, and prealbumin concentration. Nitrogen intake, postburn day, percent total body surface area burned, and age were identified as the variables that most closely correlated with nitrogen balance. None of the serum proteins entered this regression equation. The data plot (Fig. 2) showing the regression analysis of observed nitrogen balance on a predictor developed using nitrogen intake, postburn day, percent total body surface burned, and age demonstrated a better correlation ($r = 0.765$) for this predictor than for the best serum protein correlation ($r = 0.388$). Even so, the calculated predictor explains less than 60% of the observed variation in nitrogen balance and is too insensitive for clinical use.

The analyses of the relationship between change in nitrogen balance and change in serum albumin, prealbumin, retinol-binding protein, and transferrin showed all four serum visceral proteins to be poor predictors of changes in nitrogen balance. Nitrogen balance changes in the positive direction were more accurately predicted than those in the negative direction (Table IV). Changes in serum retinol-binding protein, prealbumin, and transferrin had a better correlation than serum albumin. How-

TABLE I
Patient characteristics and clinical data

Patient number	Age/sex (years)	BW (Kg)	Burn size % TBSB/% full thickness	Surgical procedures	# of times transfused	Dietary regimen	Estimated energy requirement kcal/d	% of energy requirements met		
								PBD #11	PBD #20	PBD #29
1	54/M	118	26.75/0	0	5	PO	2575	55	57	57
2	22/M	65	26/0.5	1	1	PO	3349	135	99	104
3	59/M	56	36/30	1	6	TPN/TF	3257	85	89	—
4	31/F	59.5	57/41	4	5	TF/TF + PO	2850	92	102	97
5	57/M	66	34/17.5	1	1	PO	3623	79	69	76
6	62/M	60.5	33.5/23.5	2	6	TF	3397	76	92	73
7	29/M	102	69.5/10.5	2	7	PO/TF/TPN	5640	72	73	76
8	25/M	119	27.5/5	0	0	PO	4099	89	103	97
9	20/M	79.5	48.5/48.5	5	15	TF/TPN/TF	4378	67	75	72
10	25/M	68	29.25/8.75	2	5	TF/PO	3856	103	100	92

M, male; F, female.

PO, oral diet; TPN, total parenteral nutrition; TF, tube feeding.

TABLE II
Patient population characteristics

Age	38.4 ± 17.2 years (range 20–60 y)
Burn size	38.8 ± 14.7 (range 20–69.5% TBSA)

Assessment of medical conditions:

Healthy prior to injury: patients #2, 4, 5, 7, 8, 9, 10

Complicating conditions: patients #1, 3, 6

Adequacy of dietary intake:

Met >80% of estimated requirement: 6 patients

Met >70% but <80% of estimated requirement: 3 patients

Met <70% of estimated requirement: 1 patient

TABLE III
Nitrogen balance data

Patient #	Intake* (g)/Balance† (g)			
	PBD #5	PBD #11	PBD #20	PBD #29
1	9.1/–13	12.3/–4.3	7.5/–3.5	8.2/+0.8
2	13.9/+1.8	26.4/+3.6	20.2/–2.1	18.6/–9.6
3	3.4/–18.9	17.4/+0.7	15.8/–3.5	—
4	3.0/–29.5	19.2/–7.6	15.0/–6.4	13.0/–3.0
5	0/–16	17.4/–8.1	12.3/+1.2	15.4/+3.8
6	0/–17.1	3.0/–7.8	15.8/–11.3	14.2/0
7	18.7/–29.9	20.0/–18.9	25.9/+7.9	32.6/+16.1
8	13.6/–15.3	15.5/–10.5	24.8/+5.3	21.9/+9.8
9	4.5/–22.6	19.8/–17.2	0/–20.3	20.0/+9.4
10	6.1/–13.5	23.8/+4.9	23.4/–10.1	18.7/+2.2

* Intake = quantity of nitrogen consumed or administered over 24-hour period.

† Nitrogen Balance = nitrogen intake – nitrogen loss (urinary loss + intestinal loss + wound loss).

ever, even retinol-binding protein, which had the highest number of correct predictions, corresponded to positive nitrogen balance changes in only 57% of these cases. The percentages of correct positive balance change predictions for the other proteins were 55% for prealbumin, 51% for transferrin, and 23% for albumin. Prediction of nitrogen balance changes in the negative direction was worse. Percentages of correct positive balance changes were 30% for prealbumin, 29% for transferrin, 24% for retinol-binding protein, and 5% for albumin. Thus, the overall efficiencies were less than 50% for each of the four visceral proteins.

DISCUSSION

To use serum protein levels as a basis for nutritional monitoring in patients with thermal injury, one must

recognize deviations which occur in these measurements secondary to thermal injury. Serum albumin levels are decreased following burn injury due to increased loss of albumin into the burn wound, although total albumin synthesis rates are increased.⁷ Additionally, serum albumin levels may be affected by treatment measures or by complications which may occur. For example, exogenous infusion of albumin may artificially raise the serum albumin concentration. Serum transferrin is decreased following burn injury and blood loss or blood transfusion may further alter this serum level.⁸ Decreases in prealbumin and retinol-binding protein have been described following injury.⁹ Other proteins such as serum IgG are lowest within 48 hours following thermal injury and subsequently rise to normal and supranormal levels over a 2- to 4-week period.^{10,11}

Our results demonstrate that none of the serum visceral proteins that we measured can be used to predict nitrogen balance in patients with thermal injury. This agrees with Starker et al¹ who found that serum albumin did not predict nitrogen balance changes during depletion and repletion with total parenteral nutrition, and with McCauley and Brennan¹² who found no change in serum albumin levels in cancer patients receiving total parenteral nutrition. In view of the long half-life of albumin these results are not surprising. We had expected that the shorter half-lives of prealbumin, transferrin, and retinol-binding protein might make them better indicators of nitrogen balance in this population. Although we did find statistically significant correlations between nitrogen balance and each of these protein concentrations, their large statistical variances preclude using these measures as proxies for nitrogen balance. The wide scatter of individual points did not even allow reliable prediction of whether an individual patient's nitrogen balance was positive or negative. These results are consistent with those of Shenkin et al⁹ who found no difference in serum visceral protein levels in trauma patients receiving supplemental amino acids compared to those not receiving amino acids.

The attempt to correlate change in direction of nitrogen balance with change in direction of the serum visceral protein concentrations was not successful. Fewer than one-half of positive and negative changes in nitrogen

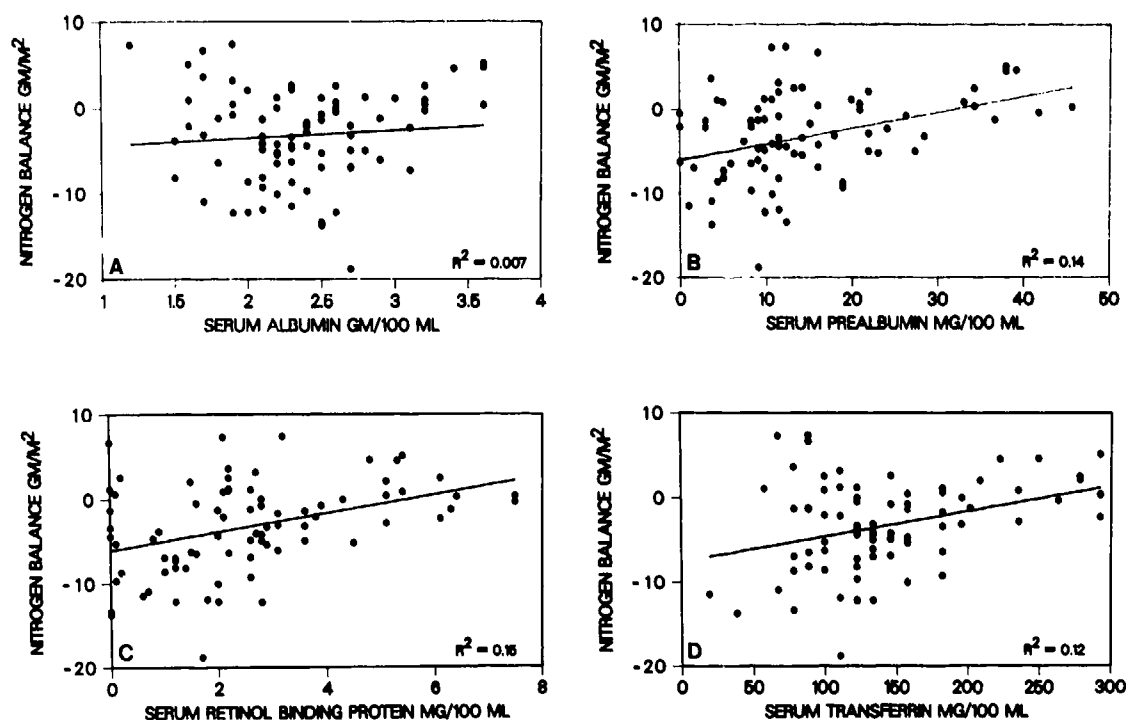


FIG. 1. Nitrogen balance vs serum visceral protein concentrations. Correlations between nitrogen balance and serum prealbumin, retinol-binding protein, and transferrin were statistically significant, but the large statistical variances demonstrated in these scatter plots preclude prediction of nitrogen balance from measures of any of these proteins.

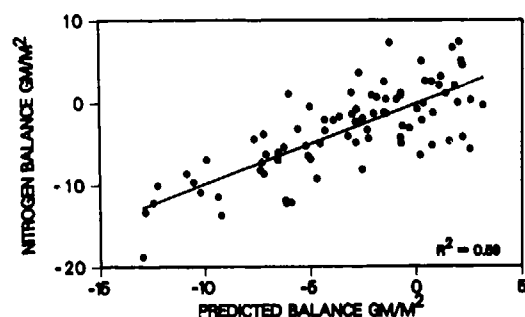


FIG. 2. Nitrogen balance vs nitrogen balance predictor based on nitrogen intake, postburn day, percent total body surface burned, and age. A factor using readily available variables selected in stepwise multiple regression analysis as most closely correlated with nitrogen balance was used to predict nitrogen balance. The correlation of this predictor with measured nitrogen balance was better than that for any of the serum visceral proteins.

balance were accurately predicted by corresponding changes in any of the serum visceral protein concentrations.

Our results show that the serum visceral proteins, which are expensive to measure, are less effective than other readily available predictors of nitrogen balance. Prices quoted by commercial laboratories for performing serum visceral protein assays were:

Prealbumin = \$26.00–\$60.00 per test

Retinol-binding protein = \$26.00–\$67.00 per test

Transferrin = \$17.50–\$69.00 per test

Monitoring serum visceral protein levels on a weekly basis would be expensive. For example, monitoring preal-

TABLE IV
Prediction of nitrogen balance using correlation of change in nitrogen balance with change in serum visceral protein concentrations

Serum visceral protein	Correct predictions*		Efficiency† (%)
	Positive balance	Negative balance	
Albumin	10/44	1/21	17
Prealbumin	23/42	6/20	47
Retinol-binding protein	24/42	5/21	46
Transferrin	22/43	6/21	44

* Correct prediction = change of serum visceral protein in same direction as nitrogen balance/total number of nitrogen balance changes.

† Efficiency = correct prediction/total nitrogen balance changes × 100.

bumin and transferrin once a week would cost approximately \$80/wk/patient, using the average cost based upon quotes from the five laboratories. In view of the poor predictive value of these measures, this expense does not seem warranted. Moreover, a calculated "predictor" based on use of nitrogen intake, percent total body surface area burned, postburn day, and age predicted nitrogen balance better than did serum albumin, prealbumin, transferrin, or retinol-binding protein concentrations.

Based upon the results of this study as well as a review of the current literature, the use of serum visceral protein concentrations as indicators or predictors of nitrogen balance in thermally injured patients is unwarranted and expensive.

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